IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Sauvageau et al.		
Docket No.:	FC 14518-24	Confirmation No.	7319
Serial No.:	10/727,580	Group Art:	1636
Filing Date:	December 05, 2003	Examiner:	Dunston, Jennifer Ann
Title:	STEM CELL EXPANSION ENHANCING FACTOR AND METHOD OF USE		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

Dear Sir:

1. I, Keith Humphries, M.D., Ph.D. am a co-inventor of the above-cited application.

2. I am a Senior Scientist at the British Columbia Cancer Agency and a Professor of Medicine at the University of British Columbia.

3. I have been working in the field of self-renewal and multipotential differentiation capacity of hematopoietic stem cells (HSCs) since at least as early as 1975 and was the first to demonstrate *in vitro* self-renewal of such cells (see Humphries RK, Jacky PB, Dill FJ, Eaves AC, Eaves CJ. CFU-S in individual erythroid colonies derived in vitro from adult mouse marrow. Nature. (1979) 279 :718-20; Humphries RK, Eaves AC, Eaves CJ. Self-renewal of hemopoietic stem cells during mixed colony formation in vitro. Proc Natl Acad Sci U S A. (1981) 78:3629-33; and Fraser CC,

Eaves CJ, Szilvassy SJ, Humphries RK. Expansion in vitro of retrovirally marked totipotent hematopoietic stem cells.Blood. 1990 76:1071-6).

4. Since 1990, I have focused on the Hox homeobox family of transcription factors as candidate intrinsic regulators of normal primitive hematopoietic cell properties. Please find enclosed a copy of my resume and a list of my publications for the last five years.

Failure of others

5. Failures are rarely reported in the literature and I am thus not aware of a publication reporting a failed attempt to achieve a non-gene delivery of HOXB4 in HSCs.

6. This gene's ability to expand HSCs by retroviral gene transfer and the advantages of non-gene delivery have been known for years however. Yet, I am not aware of any success in a non-gene delivery of HOXB4 in any cells before we successfully produced a non-gene delivery transfer of HOXB4 in HSCs.

7. Hence in 1995, the other co-inventor, Guy Sauvageau, and I published a paper reporting the effect of HOXB4 on the proliferation and/or differentiation of HSCs. We had engineered the overexpression of HOXB4 in murine bone marrow cells by retroviral gene transfer and showed a greatly enhanced ability of HOXB4-transduced bone marrow cells to expand HSCs as compared with control cells.

8. Following the publication of this paper, over fifty laboratories around the world requested and obtained a sample of our HOXB4 cDNA constructs. The laboratories that received our samples include those of Sean Morrison, Irving Weissman, Hans-Peter Kiem and David Williams in the USA; Christopher Baum and Wolfram Ostertag in Germany; Roger

Pederson in the UK; Stefan Karlsson in Sweden; and Philippe Leboulch in France.

9. These laboratories all possess experience in techniques of stem cell expansion, and although several of these laboratories have reproduced our findings of stimulation of stem cell expansion by retroviral gene transfer of HOXB4, none have reported success with a non-gene delivery method. (see for example: Friel J, Schiedlmeier B, Geldmacher M, Ostertag Stromal cells selectively reduce the growth advantage of human committed CD34+ hematopoietic cells ectopically expressing HOXB4.Growth Factors. (2006) 24:97-105; Bowles KM, Vallier L, Smith JR, Alexander MR, Pedersen RA. HOXB4 overexpression promotes hematopoietic development by human embryonic stem cells. Stem Cells. (2006) 24:1359-69; Miyake N, Brun AC, Magnusson M, Miyake K, Scadden DT, Karlsson S. HOXB4-induced self-renewal of hematopoietic stem cells is significantly enhanced by p21 deficiency. Stem Cells. (2006) 24:653-61; and Ilat S, Carotta S, Schiedlmeier B, Kamino K, Mairhofer A, Will E, Modlich U, Steinlein P, Ostertag W, Baum C, Beug H, Klump H. HOXB4 enforces equivalent fates of ES-cell-derived and adult hematopoietic cells. Proc Natl Acad Sci U S A. (2005) 102:12101-6).

10. The potential disadvantages of retroviral gene transfer of Hox transcription factors such as the risk of leukemogenesis and thus corresponding advantages of protein delivery of Hox proteins such as HOXB4 were known at least as early as 1993 (e.g. see Perkins AC, Cory S. Conditional immortalization of mouse myelomonocytic, megakaryocytic and mast cell progenitors by the Hox-2.4 homeobox gene. EMBO J. (1993) 12:3835-46).

11. Yet, to my knowledge, none of the laboratories who received our samples has reported success in a non-gene transfer delivery using HOXB4.

Unpredictability

12. Guy Sauvageau and I initiated the research that would result in successful non-gene delivery of HOXB4 in hematopoietic stem cells (HSCs) described in the instant application on or about 1990.

13. To our knowledge, we were the first to successfully use the TAT motif to transfer a protein into HSCs. To our knowledge, we were also the first to achieve non-gene delivery of an expansion factor in a cell.

14. Four to six months were necessary to generate the first TAT-HOXB4 protein. Hurdles to overcome in this research program included methods of production, purification and storage, dosage (amount and frequency); *in vitro* conditions, and nature and characterization of starting cells that would respond.

15. Method of production and purification: the HOXB4 protein is poorly soluble and comprises an unusual proline-rich stretch; therefore methods had to be adapted for purifications from large volumes of cultures initiated with specialized bacterial strain engineered for production of such proteins. Recombinant HOXB4 protein remains soluble only at relatively low concentrations, and all purification steps had to be adjusted to large volumes of diluted solutions. The range of effective doses was first determined by estimating the relative amount of cellular protein isolated from HOXB4 retrovirus-transduced bone marrow cells recognized by the HOXB4 antibody, and by the ability of known amounts of recombinant HOXB4 to support the *in vitro* expansion of clonogenic progenitors.

16. Development of the methodology and generation of the initial bioactive TAT-HOXB4 protein required over 1.5 person years of work and involved a team that included a senior post-doctoral fellow (4 months, full time); 1

junior post-doctoral fellow (1 month); 1 graduate student (6 months, full time); and 2 highly experienced research assistants (over 1 month each).

17. A further six to eight months was necessary to generate the first data showing that TAT-HOXB4 can induce HSC expansion *in vitro* and support the following *in vivo* reconstitution of the hematopoietic compartments. The time required for this part of the analysis reflects the time required to accurately enumerate the numbers of the hematopoietic stem cells present in the transplanted sample (4 months each experiment), and to perform 3 independent experiments with 3 different batches of recombinant HOXB4.

18. I further declare that all statements made herein are of my own knowledge and are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

April 15, 2008
Date

Keith Humphries

Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

PROTECTED WHEN COMPLETED

Personal Identification Number (P.I.N.)

23201

CV Module

This page is for CIHR use only. It will not be included in the evaluation of your application for funding.

Family Name	Given Name	Middle Initial(s)
Humphries	Richard	K

Have you previously applied to CIHR for funding? Yes [X] No [ ]

Previous family name used: N/A

Previous given name used:

Title: Dr. [X] Mr. [ ] Mrs. [ ] Ms. [ ] Prof. [ ]

Courier Address
(If different from mailing address)

Terry Fox Laboratory
11th Floor - 675 West 10th Avenue
Vancouver, British Columbia
CANADA (V5Z 1L3)

Temporary Address

Start Date
End Date

Primary Affilliation Name

BC Cancer Agency

Start Date 01/1984

Primary Affiliation Address

Terry Fox Laboratory
11th Floor - 675 West 10th Avenue
Vancouver, British Columbia
CANADA (V5Z 1L3)

Contact numbers

Phone

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Secondary 1 (604) 675-8000 #7771 Lab

Temporary

Start Date End Date

Fax

Primary 1 (604) 877-0712

Temporary

Start Date End Date

Electronic Addresses

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khumphri@bccrc.ca

Web page address
http://www.bccrc.ca/tfl/people_khumphri.html

Citizenship

Canadian [X] Other [ ]

Other Country of Citizenship

Permanent Residence in Canada

Permanent Resident [ ] Date of permanent residency status DD/MM/YYYY

Have you applied for permanent residency? Yes [ ] No [ ]

Correspondence Language

English [X] French [ ]

Language	Read	Write	Speak	Understand
English (Yes or No)	YES	YES	YES	YES
French (Yes or No)	NO	NO	NO	NO

Other Languages:

Gender

Male [X] Female [ ]

Date of Birth (DD/MM/YYYY)

05/12/1948

Signature Date

Expertise

List up to ten (10) key words that best describe your expertise in research, instruments and technique.

hematopoiesis	transcription factors
leukemia	transgenic mice
stem cells	gene targeting
retroviral gene transfer	Hox genes
gene therapy	embryonic stem cells

Indicate and rank the disciplines that best correspond to your research interests. No additional pages may be added.

	Discipline		Sub Discipline	
Rank	**Code**	**Description**	**Code**	**Description**
1.	52	HEMATOLOGY	642	Leukemias
2.	13	CANCER/ONCOLOGY	489	Genomics
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				

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Academic Background - One additional page may be added

Indicate all university degrees obtained and those in progress (where applicable) starting with the most recent. If you hold a co-degree from more than one institution (e.g. under the Soutien aux cotutelles de these de doctorat agreement between Quebec and France) enter each institution separately. Do not enter honorary degrees here, they should be listed in the Distinctions section.

Also indicate research training, such as postdoctoral or fellowship training. Trainees only: also list undergraduate and graduate research training experience.

Degree Type	Degree Name and Specialty	Institution/Organization and Country	Supervisor name	Start date (MM/YYYY)	Date received or expected (MM/YYYY)
Doctorate (PhD)	Doctor of Philosophy Medical Genetics	The University of British Columbia CANADA	CJ Eaves	09/1976	06/1980
Doctor (Medical)	Doctor of Medicine No specialty	The University of British Columbia CANADA	N/A	09/1971	05/1975
Master's	Masters of Science Medical Biophysics	University of Toronto CANADA	RG Miller	07/1970	08/1972
Bachelor's, Honours	Bachelor of Science Physics	University of Alberta CANADA	N/A	09/1966	05/1970

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Work Experience

Starting with the most recent, indicate your current position, where applicable, and other academic and non-academic position(s) since the beginning of your university studies. For your current positions leave the end date blank. Additional pages will be accepted.

Position	Institution/Organization and Country	Department/Division and Faculty/School	Start Date (MM/YYYY)	End Date (MM/YYYY)
Full Professor	The University of British Columbia CANADA	Medicine Medicine	01/1994	
Associate Member	The University of British Columbia CANADA	Pathology and Laboratory Medicine Medicine	01/1984	
Associate Member	The University of British Columbia CANADA	Medical Genetics Medicine	01/1984	
Scientist	BC Cancer Agency CANADA	Terry Fox Laboratory N/A	01/1984	
Associate Professor	The University of British Columbia CANADA	Medicine Medicine	01/1989	01/1994
Assistant Professor	The University of British Columbia CANADA	Medicine Medicine	01/1984	01/1989
Research Associate	National Heart, Lung and Blood Institute UNITED STATES	Clinical Hematology Branch N/A	07/1980	12/1983

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Distinctions / Awards / Credentials

Starting with the most recent, indicate any recognitions received, including awards, fellowships, scholarships, licenses, qualifications, professional designation or credentials. Do not include Academic Appointments here, as they are detailed under Work Experience. Maximum 20 entries.

Name/Title and Type	Institution/Organization and Country	Effective Date (MM/YYYY)	End Date (MM/YYYY)	Specialty	Total Amount
Research Prize (Sr. Science Category) Distinction	UBC Izaak Walton Killam CANADA	02/2003		Medical and Health Sciences	$5,000
MRC Award Research award	Medical Research Council of Canada CANADA	05/1985			
Member Credential	College of Physicians & Surgeons BC CANADA	12/1976			
Licentiate Credential	Medical Council of Canada CANADA	11/1976			
MRC Award Research award	Medical Research Council of Canada CANADA	09/1976			
Medical Prize Research award	British Laboratories CANADA	09/1973			
Medical Award Research award	The Max & Susie Dodek Medical Scholarship CANADA	09/1973			
Award Research award	The Parke, Davis & Company Ltd. CANADA	09/1973			
Osler Award Research award	The Hamish McIntosh Memorial Prize of UBC CANADA	05/1973			
Postgraduate Award Research award	University of BC Medical School CANADA	09/1970			

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Distinctions / Awards / Credentials

Starting with the most recent, indicate any recognitions received, including awards, fellowships, scholarships, licenses, qualifications, professional designation or credentials. Do not include Academic Appointments here, as they are detailed under Work Experience. Maximum 20 entries.

Name/Title and Type	Institution/Organization and Country	Effective Date (MM/YYYY)	End Date (MM/YYYY)	Specialty	Total Amount
Postgraduate Award-Centennial Scholarship Research award	National Research Council of Canada CANADA	07/1970			
Gold Medal in Physics Research award	Louis S. Crosby Memorial CANADA	05/1970			
Award (First Class Standing Prize) Research award	University of Alberta CANADA	09/1969			
University Award Research award	Board of Governors of the University Scholarship in Science CANADA	09/1968			
Honor Prize Research award	University of Alberta CANADA	09/1967			
Award Research award	Federated Pipe Lines Ltd. CANADA	09/1966			
Matriculation Prize Research award	Assoc. of Professional Engineers of Alberta CANADA	09/1966			

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Patents and Intellectual Property Rights

Record the total numbers of patents / copyrights in the following table.

OBTAINED			APPLICATIONS UNDER PROCESS			TOTAL PATENTS AND INTELLECTUAL PROPERTY RIGHTS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
1	2	3	0	5	5	8

PUBLICATIONS AND PRESENTATIONS

Give the number of publications and presentations in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

Publications	Refereed Articles	Books and Monographs	Proceedings / Book Chapters / Contributions to a collective work	Abstracts / Notes	TOTALS
Already Published	165	0	54	331	550
Accepted or in the Press	1	0	1	0	2
					552

Invited presentations	145

LITERARY AND ARTISTIC WORKS

Provide the number of literary and artistic works created in the course of your career. Detailed information should be attached as specified in the "Contributions - details" section.

IN CIRCULATION			IN PROGRESS			TOTAL LITERARY AND ARTISTIC WORKS
Total individual	Total collective	Sub-total	Total individual	Total collective	Sub-total	
0	0	0	0	0	0	0

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Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 1 Doctoral 2 Post-Doctoral 7

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.
* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
*	Gyeongsin Park	Postdoctoral Fellow, Health Professional	03/2008				Properties of Leukemic Stem Cells	Postdoctoral Fellow, Terry Fox Lab, BCCA
*	Ping Xiang	Postdoctoral Fellow, PhD	05/2007				Function of PBXIP1 in Leukemia	Postdoctoral Fellow, Terry Fox Lab, BCCA
*	Michelle Miller	Graduate Student	10/2006				Hematopoietic Stem Cell Self-renewal: Mechanisms and Manupulation	MSc Grad Student, Med Genetics, UBC
*	Michael Heuser	Postdoctoral Fellow, Health Professional	01/2006				Role of Novel Regulator MN1 in Leukemia	Postdoctoral Fellow, Terry Fox Lab, BCCA
*	Shin-Ichiro Kawamoto	Postdoctoral Fellow, Health Professional	01/2006				Approaches to HSC Expansion	Postdoctoral Fellow, Terry Fox Lab, BCCA
*	Florian Kuchenbauer	Postdoctoral Fellow, Health Professional	09/2005				Hox Genes in Leukemia	Postdoctoral Fellow, Terry Fox Lab, BCCA
*	Sanja Sekulovic	Graduate Student	09/2005				Mechanisms of Self-renewal	PhD Student, Med Genetics UBC
*	Eric Yung	Postdoctoral Fellow, PhD	03/2005				Novel Strategies for Genetic Modification and Expansion of Hematopoietic Stem Cells	Postdoctoral Fellow, Terry Fox Lab, BCCA

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Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 1 Doctoral 2 Post-Doctoral 7

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* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
*	Bob Argiropoulos	Postdoctoral Fellow, PhD	12/2003				Meis1 in Normal and Leukemic Hemopoiesis	Postdoctoral Fellow, Terry Fox Lab, BCCA
*	Nooshin Tabatabaei	Postdoctoral Fellow, Health Professional	05/2007	01/2008			Differentiation of Embryonic Stem Cells into Hematopoietic Stem Cells	Researcher, StemCell Technologie
*	Silvia Bakovic	Graduate Student	09/2000	07/2007	Doctorate (PhD)	2007	Stem Cell Expansion for Gene Therapy	PhD Grad Student, Med Genetics, UBC
*	Fredrik Rook	Graduate Student	01/2005	12/2005			Mechanisms of Leukemic Transformation	MBA Student, SFU
*	Sanja Sekulovic	Graduate Student	12/2003	09/2005	Master's	2005	Expansion of Stem Cells	MSc Grad Student, Med Genetics, UBC
*	Koichi Hirose	Postdoctoral Fellow, Health Professional	04/2003	04/2005			Molecular Mechanism Linking Hox Transcription Factors to Leukemia	Staff Clinician, Chiba Univ., Japan
*	Rhonna Gurevich	Graduate Student	08/2000	04/2005	Doctorate (PhD)	2005	The Role of NUP98 Fusion Proteins in Leukemia	Postdoctoral Fellow, StemCell Technologie
*	Lars Palmqvist	Postdoctoral Fellow, Health Professional	10/2002	12/2004			Genes Regulated by Hox-induced Leukemias	Staff Clinician, Gotteberg U. Sweden

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Supervisory Experience: To be completed by applicants requesting research trainees as part of their budget, salary support candidates and proposed supervisors of trainees.

Indicate the number of graduate students and postdoctoral fellows that you currently supervise or co-supervise. CIHR defines supervisory experience as the formal supervision or co-supervision of trainees. Enter zero (0) if not applicable.

Master 1 Doctoral 2 Post-Doctoral 7

Complete this form by listing the trainees that you have supervised/co-supervised (and are currently supervising/co-supervising) within the last five (5) years. Additional pages may be added if necessary.
* Flag those where you were/are the Primary Supervisor.

*	Name of Student	Program Type	Dates		Degree received or expected	Year Degree Rec'd (YYYY)	Research Project (Short title)	Current position and Institution
			Support Period From (MM/YY	To (MM/YYYY)				
*	Hideaki Ohta	Postdoctoral Fellow, Health Professional	10/2001	09/2004			Embryonic Stem Cell Models to Study Normal and Leukemic Hematopoiesis	Head, Pediatric Hema, Osaka U. Japan
*	Nicolas Pineault	Postdoctoral Fellow, PhD	10/2001	06/2004			HOX Genes in Early Hematopoietic Development & Leukemia	Scientist, Hema-Quebec U. Laval
*	Carolina Abramovich	Postdoctoral Fellow, PhD	09/1996	12/2003			Leukemogenesis	Project Manager, Globel Laboratories

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Funds REQUESTED

List all sources of support applied for (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount requested (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Engineered Advances for Clinical Applications of Gene Therapy		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Team Grant	
Principal Applicant / Project Leader Piret, Jamie	**Your Role** Co-Applicant	
Total Amount (CAN$) $544,602	**Support Period From (MM/YYYY)** 04/2008	**To (MM/YYYY)** 03/2011

Title of Proposal Microfluidic Systems to Accelerate Mammalian Cell Bioprocess Research and Development		
Funding Source Natural Sciences and Engineering Research Council of Canada (NSERC)	**Program Name** Research Tools and Instruments - Category 1	
Principal Applicant / Project Leader Piret, Jamie	**Your Role** Co-Applicant	
Total Amount (CAN$) $142,433	**Support Period From (MM/YYYY)** 03/2008	**To (MM/YYYY)** 02/2009

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Determinants of Leukemic Stem Cell Origin and Function		
Funding Source National Cancer Institute of Canada (NCIC)	**Program Name** Group Grant	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $929,550	**Support Period From (MM/YYYY)** 10/2007	**To (MM/YYYY)** 09/2012

Title of Proposal CIHR Team on Analysis of Stem Cells Using a New High-Throughput Technology for Interrogating the Molecular Responses of Single Cells		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Team Grant Program	
Principal Applicant / Project Leader Piret, Jamie	**Your Role** Co-Applicant	
Total Amount (CAN$) $2,500,000	**Support Period From (MM/YYYY)** 01/2006	**To (MM/YYYY)** 12/2011

Title of Proposal CIHR Team in Stem Cell Expansion		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Team Grant Progam	
Principal Applicant / Project Leader Sauvageau, Guy	**Your Role** Co-Applicant	
Total Amount (CAN$) $4,400,000	**Support Period From (MM/YYYY)** 11/2006	**To (MM/YYYY)** 10/2011

Title of Proposal CIHR Team on Stem Cells for the Treatment of Bone Marrow Failure		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Genomic Medicine and Human Development Operating Grants	
Principal Applicant / Project Leader Lansdorp, Peter	**Your Role** Co-Applicant	
Total Amount (CAN$) $2,500,000	**Support Period From (MM/YYYY)** 11/2005	**To (MM/YYYY)** 10/2010

Funds CURRENTLY HELD

List all sources of support currently held (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Leukemogenic Properties of the Potent Oncogene MN1		
Funding Source Cancer Research Society (The)	**Program Name** Operating	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $120,000	**Support Period From (MM/YYYY)** 09/2007	**To (MM/YYYY)** 09/2009

Title of Proposal MicroRNAs as Therapeutic Agents in Acute Myeloid Leukemia		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating Grant: Proof of Principle	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $138,655	**Support Period From (MM/YYYY)** 04/2008	**To (MM/YYYY)** 04/2009

Title of Proposal HOXB4 is an Activator of HSC Self-Renewal		
Funding Source National Institutes of Health (NIH) (USA)	**Program Name** Operating	
Principal Applicant / Project Leader Sauvageau, Guy	**Your Role** Co-Applicant	
Total Amount (CAN$) $1,743,902	**Support Period From (MM/YYYY)** 05/2005	**To (MM/YYYY)** 04/2009

Title of Proposal		
Funding Source	**Program Name**	
Principal Applicant / Project Leader	**Your Role**	
Total Amount (CAN$)	**Support Period From (MM/YYYY)**	**To (MM/YYYY)**

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Cell Therapy for Muscular Disease		
Funding Source Networks of Centres of Excellence (NCE)	**Program Name** Stem Cell Network	
Principal Applicant / Project Leader Rossi, Fabio	**Your Role** Co-Applicant	
Total Amount (CAN$) $96,000	**Support Period From (MM/YYYY)** 09/2005	**To (MM/YYYY)** 03/2008

Title of Proposal Development of Technologies for the Derivation, Propagation and Differentiation of hESC		
Funding Source Networks of Centres of Excellence (NCE)	**Program Name** Stem Cell Network	
Principal Applicant / Project Leader Piret, Jamie	**Your Role** Principal Applicant	
Total Amount (CAN$) $37,952	**Support Period From (MM/YYYY)** 09/2005	**To (MM/YYYY)** 03/2008

Title of Proposal Cancer Stem Cell Genomics and Theraputics		
Funding Source Networks of Centres of Excellence (NCE)	**Program Name** Stem Cell Network	
Principal Applicant / Project Leader Hassell, John A	**Your Role** Co-Applicant	
Total Amount (CAN$) $40,000	**Support Period From (MM/YYYY)** 01/2007	**To (MM/YYYY)** 01/2008

Title of Proposal Genetic Determinants of Stem Cell Function (Project 5 of Program Project: Normal and Leukemic Hemopoiesis)		
Funding Source National Cancer Institute of Canada (NCIC)	**Program Name** Operating Group Grant	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $857,675	**Support Period From (MM/YYYY)** 07/2002	**To (MM/YYYY)** 06/2007

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal Novel Agents for Hemotopoietic Stem Cell Expansion		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Proof of Principle Grant	
Principal Applicant / Project Leader	**Your Role** Principal Applicant	
Total Amount (CAN$) $133,018	**Support Period From (MM/YYYY)** 09/2005	**To (MM/YYYY)** 08/2006

Title of Proposal HOXB4 Target-genes Specifying Hematopoietic Stem Cell Renewal		
Funding Source Networks of Centres of Excellence (NCE)	**Program Name** Stem Cell Network	
Principal Applicant / Project Leader Sauvageau, Guy	**Your Role** Co-Applicant	
Total Amount (CAN$) $472,745	**Support Period From (MM/YYYY)** 01/2003	**To (MM/YYYY)** 04/2006

Title of Proposal Gene Discovery in Stem Cells (StemNET)		
Funding Source Networks of Centres of Excellence (NCE)	**Program Name** The Stem Cell Network	
Principal Applicant / Project Leader Worton, Ron	**Your Role** Co-Applicant	
Total Amount (CAN$) $541,745	**Support Period From (MM/YYYY)** 10/2001	**To (MM/YYYY)** 03/2006

Title of Proposal Gene Therapy for Sickle Cell Anemia		
Funding Source National Institutes of Health (NIH) (USA)	**Program Name** Operating	
Principal Applicant / Project Leader Nagel, Ron	**Your Role** Co-Applicant	
Total Amount (CAN$) $2,454,832	**Support Period From (MM/YYYY)** 09/2000	**To (MM/YYYY)** 08/2005

Funds HELD IN THE LAST FIVE YEARS

List all sources of support held in the last five years (including CIHR) as an applicant or as a co-applicant. Include the principal applicant's name, title of the proposal, funding source, program name, total amount awarded (in Canadian dollars) and the period of the support. Indicate your role in the funding (principal applicant/project leader or co-applicant).

Title of Proposal HOXB4: A Hemopoietic Stem Cell Expanding Factor		
Funding Source National Institutes of Health (NIH) (USA)	**Program Name** Operating	
Principal Applicant / Project Leader Sauvageau, Guy	**Your Role** Co-Applicant	
Total Amount (CAN$) $412,692	**Support Period From (MM/YYYY)** 07/2001	**To (MM/YYYY)** 06/2005

Title of Proposal Cancer Genomics in Early Stage Cancers		
Funding Source Genome British Columbia	**Program Name** Operating	
Principal Applicant / Project Leader Ling, Victor & Marra, Marco & Eaves, Connie	**Your Role** Co-Applicant	
Total Amount (CAN$) $314,098	**Support Period From (MM/YYYY)** 09/2001	**To (MM/YYYY)** 03/2005

Title of Proposal Roles of G Protein-coupled Receptors in Hemopoeisis and Leukemogenesis		
Funding Source Canadian Institutes of Health Research (CIHR)	**Program Name** Operating	
Principal Applicant / Project Leader Kay, Robert	**Your Role** Co-Applicant	
Total Amount (CAN$) $586,675	**Support Period From (MM/YYYY)** 10/1999	**To (MM/YYYY)** 09/2004

Title of Proposal Role of Homeobox Genes in Early Hematopoiesis		
Funding Source National Institutes of Health (NIH) (USA)	**Program Name** Operating	
Principal Applicant / Project Leader Lawrence, Jeff	**Your Role** Co-Applicant	
Total Amount (CAN$) $254,856	**Support Period From (MM/YYYY)** 09/2000	**To (MM/YYYY)** 08/2004

Details of Funds Requested and Currently Held - Instruction Page

All applicants must complete the Funding section which is common to all member agencies. This will populate the CV Module, Pages 8-10 (a, b, c, etc.). All applicants, with the exception of training award candidates and their supervisors, must attach the "Details of funds currently requested or currently held" pages numbered 11a, 11b, 11c, etc. (See items A and B below).

FILE ATTACHMENT - General Instructions

The following format should be adhered to for this attachment.
- 8.5" X 11" (21.5 X 28.0 cm) white single-sided paper.
- Margins of ¾" (2 cm).
- Minimum font size 12 point or 10 characters per inch.
- Six lines per inch, single-spaced, with no condensed type or spacing.
- Each page header must contain your name, the application submission date and the sub-section header, i.e., Funding - CIHR.
- Please note that as of November 2004, the "Details of funds currently requested or currently held" pages should be numbered 11a, 11b, 11c, etc.

A) All grant applicants should attach one page with the following information for each grant applied to or currently held as principal applicant or co-applicant.

1. Title of proposal
2. Funding source and Program name
3. Hours per week
4. Budgetary overlap (%) with current application
5. Renewable (yes or no)
6. Grant number (if applicable)
7. For grants currently held, describe any changes in design or direction since the grant was awarded.
8. Describe the conceptual and budgetary relationships of this project to the proposed research.
9. List employees paid out of this grant giving their names, categories and levels of technician or types of trainee.

B) For each grant currently applied for and currently held as principal applicant or co-applicant, also attach a paper copy of the summary from the original application, including its title.

Note : You must inform CIHR of any other support requested or received during the review period of this application.

Attachment Instructions

How to prepare and format all attachments:

Most Significant Contributions, Activities/Contributions, Interruptions/Delays, Patents/Copyrights (Part 2), and Publications (Part 2) details shall be contained in a CV attachment. The following format should be adhered to for this attachment.

- 8.5" X 11" (21.5 X 28.0 cm) white single-sided paper.
- Margins of ¾" (2 cm).
- Minimum font size 12 point or 10 characters per inch.
- Six lines per inch, single-spaced, with no condensed type or spacing.
- Number pages consecutively after CV (If, for example, the print-out of the CV ends on page 8, the attachment would begin with page 9.).
- Each page header must contain the name and/or PIN, as well as the application submission date and the sub-section header, i.e., Most Significant Contributions.

Most Significant Contributions

This section applies only to researchers, not to students. Identify a maximum of five (5) contributions, with a maximum length of one page, that best highlight your contribution or activities to research, defining the impact and relevance of each. (A contribution is understood to be a publication, literary or artistic work, conference, patent or copyright, contract or creative activity, commission, etc.) Your complete description may include the organization; position or activity type and description; from and to dates; and the basis on which this contribution is significant (i.e. relevance, target community and impact).

Activities / Contributions

The activities and contributions defined in this section should include both academic and non-academic achievements, and their impacts. Attach one page.

Interruption(s) / Delays

Identify any administrative responsibilities, family or health reasons, or any other factors that might have delayed or interrupted any of the following: academia, career, scientific research, other research, dissemination of results, training, etc. Common examples of an interruption/delay might be a bereavement period following the death of a loved one, maternity/parental leave, or relocation of your research environment.

Descriptions might include the start and end dates, the impact areas, and the reason(s) or a brief explanation of the absence. Attach one page.

Patents and Copyrights

This section should include detail for patents and copyrights for technology transfer, products, and services. Do not include Publications in this section.

Descriptions for patents/copyrights might include the title, patent/copyright number and date, country(ies) of issue, as well as the relevance or impact of this item and any inventor name(s) which pertain to it. Attach one page.

Publications List

List your most important publications and other research contributions over the past five years, according to the categories below. This is not necessarily a complete list, and is only intended to provide guidance. Categories can be added as needed. Use only items pertinent to the application. **There is no limit to the number of pages you can use.**

For Training or Salary Support Awards Candidates

- Candidates for training awards or New Investigator awards should list all publications, not just those of the last five years.
- All candidates for training or salary support awards must, for each multi-authored publication, define their role in the publication and indicate their percent contribution to the team effort.
- Candidates for training awards, with or without publications, are invited to comment on environmental factors that affected their capacity to publish.
- Candidates for salary support awards should, for multi-authored publications, underline the names of trainees whose work they supervised.

For Proposed Supervisors of Training Award Applicants

- Attach a maximum of two pages listing the titles and contributions over the past 5 years that will serve the application best.

REFEREED PUBLICATIONS

1. Baran CP, Tridandapani S, Helgason CD, **Humphries RK**, Krystal G & Marsh CB. The inositol 5'-phosphatase SHIP-1 and the Src kinase lyn negatively regulate macrophage colony-stimulating factor-induced Akt activity. J Biol Chem 278: 38628-38636, 2003.

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3. Brun ACM, Fan X, Björnsson JM, **Humphries RK** & Karlsson S. Enforced adenoviral vector-mediated expression of HOXB4 in human umbilical cord blood $CD34^+$ cells promotes myeloid differentiation but not proliferation. Mol Ther 8: 618-628, 2003.

4. Crow AR, Song S, Freedman J, Helgason CD, **Humphries RK**, Siminovitch KA & Lazarus AH. IVIg-mediated amelioration of murine ITP via FcγRIIB is independent of SHIP1, SHP-1 and Btk activity. Blood 102: 558-560, 2003.

5. Feuring-Buske M, Gerhard B, Cashman J, **Humphries RK**, Eaves CJ & Hogge DE. Improved engraftment of human acute myeloid leukemia progenitor cells in beta 2-microglobulin-deficient NOD/SCID mice and in NOD/SCID mice transgenic for human growth factors. Leukemia 17: 760-763, 2003.

6. Helgason CD, Antonchuk J, Bodner C & **Humphries RK**. Homeostatis and regeneration of the hematopoietic stem cell pool are altered in *SHIP*-deficient mice. Blood 102: 3541-3547, 2003.

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10. Pineault N, Buske C, Feuring-Buske M, Abramovich C, Rosten P, Hogge DE, Aplan PD & **Humphries RK**. Induction of acute myeloid leukemia in mice by the human leukemia-specific fusion gene *NUP98-HOXD13* in concert with *Meis1*. Blood 101: 4529-4538, 2003.

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12. Gurevich RM, Aplan PD & **Humphries RK**. *NUP98-Topoisomerase I* acute myeloid leukemia-associated fusion has potent leukemogenic activities independent of an engineered catalytic site mutation. Blood 104: 1127-1136, 2004.

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14. Milsom MD, Woolford LB, Margison GP, **Humphries RK** & Fairbairn LJ. Enhanced in vivo selection of bone marrow cells by retroviral-mediated coexpression of mutant O^6 methylguanine-DNA-methytransferase and HOXB4. Mol Ther 10: 862-873, 2004.

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34. Ohta H*, Sekulovic S*, Bakovic S, Eaves CJ, Pineault N, Gasparetto M, Smith C, Sauvageau G & **Humphries RK.** Near-maximal expansion of hematopoietic stem cells in culture using NUP98-HOX fusions. Exp Hematol 35: 817-830, 2007. (*Authors contributed equally to this study).

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